Erhardtstraße 27
D-8000 München 2
☎ 089/2399-0
Tx 523656 epmu d
FAX 089/2399-4465

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Calderbank, Thomas Roger
MEWBURN ELLIS & CO.
2/3 Cursitor Street
London EC4A 1BQ
GRANDE BRETAGNE

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Datum/Date
23.12.92

Zeichen/Ref/Réf	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
IMA/100/233	84305909.8-2105/

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
GENENTECH, INC.

INTERLOCUTORY DECISION WITHIN THE MEANING OF ARTICLE 106(3) EPC

After examining the opposition(s) the Opposition Division has decided as follows:

☒ Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the EPC.

The documents on which the decision is based are indicated on sheet 2.

☐ The opposition of the opponents ..... is found to be admissible cf. Guidelines D-IV, 5.5.

The grounds for the decision are attached hereto.

Possibility of appeal

A separate appeal is allowed (Art. 106 (3) EPC).

Notice of appeal must be filed in writing at the European Patent Office within **two months** of the date of notification of the decision and a written Statement of Grounds must be filed within **four months** of that date. A fee is payable for appeal as laid down in the Rules relating to Fees. In accordance with Rule 68(2) EPC the text of Articles 106 to 108 EPC is attached hereto.

Opposition Division

(S. Yeats) Chairman | (E. Hardon) 2nd examiner | (C. Gemmiti) Primary examiner | Legally-qualified member

Enclosed: Grounds for the decision (Form 2916) (19 page(s)) + Annexes
Form 2019
Documents relating to the amended patent

Registered letter with advice of delivery

EXHIBIT F

Article 106
Decisions subject to appeal

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

(2) An appeal may be filed against the decision of the Opposition Division even if the European patent has been surrendered or has lapsed for all the designated States.

(3) A decision which does not terminate proceedings as regards one of the parties can only be appealed together with the final decision, unless the decision allows separate appeal.

(4) The apportionment of costs of opposition proceedings cannot be the sole subject of an appeal.

(5) A decision fixing the amount of costs of opposition proceedings cannot be appealed unless the amount is in excess of that laid down in the Rules relating to Fees.

Article 107
Persons entitled to appeal and to be parties to appeal proceedings

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

Article 108
Time limit and form of appeal

Notice of appeal must be filed in writing at the European Patent Office within **two months** after the date of notification of the decision appealed from. The notice shall not be deemed to have been filed until after the fee for appeal has been paid. Within **four months** after the date of notification of the decision, a written statement setting out the grounds of appeal must be filed.

Further information concerning the filing of an appeal

(a) The appeal is to be filed with the European Patent Office either at its seat in Munich, at its branch at The Hague or at its Berlin sub-office. The addresses are as follows:

(i) European Patent Office
Erhardtstraße 27
D-8000 Munich 2
Germany
(Telex: 523656 epmu d)
(Fax: 089/2399-4465)

(ii) European Patent Office
Branch at The Hague
Patentlaan 2
Postbus 5818
NL-2280 HV Rijswijk (ZH)
Netherlands
(Telex: 31651 epo nl)
(Fax: 070/340-3016)

(iii) European Patent Office
Berlin sub-office
Gitschiner Str. 103
D-1000 Berlin 61
Germany
(Fax: 030/25901-840)

(b) The notice of appeal must contain the name and address of the appellant in accordance with the provisions of Rule 26 (2)(c) EPC, and a **statement** identifying the decision which is impugned and the extent to which amendment or cancellation of the decision is requested (see Rule 64 EPC). The notice of appeal and any subsequent submissions stating the grounds for appeal must be signed.

(c) Notice of appeal must be **filed in writing** (typewritten or printed (Rule 36(2) EPC), by telegram, telex or fax (Rule 36(5) EPC; OJ 6/89 pages 219-225; OJ 9/89 page 396)).

(d) The fee for appeal is laid down in the Rules relating to Fees. The equivalents in the national currencies in which the fee for appeal can be paid are regularly published in the Official Journal of the European Patent Office under the heading "Guidance for the payment of fees, costs and prices".

☒ Blatt 2 der Zwischenentscheidung
page 2 of the interlocutory decision
page 2 de la décision intermédiare

☐ Anlage zum Protokoll vom .....
annex to the minutes of .....
annexe au procès du .....

Anmeldenummer / Application No / N° de la demande 84305909.8

4. Unterlagen für die Aufrechterhaltung in geändertem Umfang/Documents for the maintenance of the patent as amended/ Documents à remettre en vue du maintien du brevet tel qu'il a été modifié

Bei unterschiedlichen Unterlagen für verschiedene Vertragsstaaten weiteres Blatt 3 (Form 2339.3) verwenden.
Use a further sheet 3 (Form 2339.3) if there are different documents for different Contracting States.
En cas de documents différents remis pour des Etats contractants différents, utiliser une autre feuille 3 (formulaire 2339.3).

Fassung A/B für die Vertragsstaaten/Text A/B for the Contracting States/Version A/B pour les Etats contractants : .....

Beschreibung/Description :

Spalte/Seite: 3, 5 – 22 Column/page: Colonne :	der Patentschrift of the patent specification du fascicule de brevet		
Seite: 4 Page: Page :	eingegangen am received on reçue le	mit Schreiben vom with letter of avec lettre du	7/12/92
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Patentansprüche/Claims/Revendications :

Nr.: No.: N° :	der Patentschrift of the patent specification du fascicule de brevet		
Nr.: 1 – 12 (third subsid. No.: N° : request, amended)	eingegangen am received on reçue le	mit Schreiben vom with letter of avec lettre du	filed at the E.P.O. on 22/9/92
Nr.: No.: N° :	eingegangen am received on reçue le	mit Schreiben vom with letter of avec lettre du	

Zeichnung(en)/Drawing(s)/Dessin(s) :

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DECISION

concerning

European Patent No. 0 139 417

based on the European Patent Application No. 84305909.8

in the name **GENENTECH INC.**

Part I

Summary of facts and submissions

1. The EPO Bulletin 89/30 of 26.07.89 published the grant of the European Patent No.0 1394178, based on the European Patent Application No. 84305909.8, filed on 29.08.84, claiming priority of 30.08.83 (US 527917), 31.10.83 (US 547551) and 09.03.84 (US 588170)

2. Notice of Opposition was filed by the firm **CHIRON CORPORATION** with letter of 24.04.90.
The Opposition is formally based on Art. 100 (a) within the terms of Art. 54(1) and 56 EPC and Art. 100 (b).

The documents (H) to (R), attached to the Decision as Annex I, have been cited in support of the Opponent's arguments.

2.1. Opponent requested revocation of the patent to the extent of all the granted claims for lack of novelty, for lack of inventive step and because the invention cannot be repeated in all the claimed embodiments.
Oral Proceedings were further requested.

3. The Proprietor responded to the Notice of Opposition with letter of 09.01.91 and 29.01.91.
The Proprietor's arguments were accompanied and supported by the further references S, T, U (see Annex I) and by the Declarations of J.K. Rose, J.K. Skehel and

D.S.Secher.
A new set of 14 amended claims was filed.
Maintenance of the patent in amended form and
Oral proceedings as auxiliary means were requested.

4. The Opponent's position was further corroborated by the letter of 23.12.91 comprising the additional document V (see Annex I) and by the Declaration of R.L. Burke of 20.03.92 accompanied by exhibit B (Nature, V.298, 1 July 1982, pp 30-33), exhibit C (PNAS USA, V.80, April 1983, pp 2365-2369 and exhibit D (PNAS USA, V.79, January 1982, pp 569-573).

5. The Examining Division sent a communication on 04.03.92, wherein the newly filed amended claims were objected to under Art. 123(2) and (3) EPC.

6. Oral Proceedings were held before the Opposition Division on 22.09.92.
During the proceedings the Proprietor filed four amended sets of claims.
Claims according to the main request and to the first and second subsidiary requests were objected to by the Division under Art. 123(3).
The claims of the third subsidiary request were regarded as allowable under Art 123 (2) and (3) EPC.
During the proceedings claims 10 and 11 of the latter request were further modified (fourth subsidiary request). Said modified set of claims was maintained as the new request for the maintenance of the patent in amended form by the Proprietor who abandoned, without any prejudice, all the previous set of claims.

The new reference (W) (see Annex I) was presented by the Opponent and considered by the Division pursuant Art. 114 (1) EPC because there was a likelihood that the

document could have an influence on the outcome of the proceedings.

7. The text of claims 1 to 12 for which the present Decision is issued is appendant hereto as Annex II.

8. Summary of the arguments:

8.1. Novelty of the product claims 1 to 9 was objected to by the Opponent on the basis of the teaching in references N, K, H, I, J and W, which all disclose the expression and the secretion in culture medium of truncated membrane-free derivatives of membrane-bound viral polypeptides.

In the Opponent's opinion the wording of claim 1, specifically the word "transfected" and the expression "DNA encoding said derivative" have no clear meaning, so that also natural processes like those of N and K, which disclose the natural secretion of gD and gC fragments from HSV infected cells, or any other natural process of secretion of polypeptide derived from a broader precursor (see HIV gp160/gp120) should be considered identical to the process of the opposed patent.

The property of raising neutralizing protective antibodies upon in vivo challenge by a viral pathogen, which is a condition provided by claim 1, is considered by the Opponent as an inherent feature of any secreted polypeptides, which therefore cannot represent whatever limitation or definition for the process itself.

8.2. Should, on the contrary, the ability of raising in vivo protective antibodies be regarded as a characterizing feature of the process, said process would lack inventive step since the use of the truncated peptides for

the formulation of vaccines is suggested by reference H or, alternatively, since testing the immunogenicity of a peptide is within the competence of the skilled person.

In support of this latter opinion, the Opponent cited reference L and exhibits B, C and D (accompanying R.L.Burke's Declaration) which report short synthetic peptides derived from HSV gD (L) or other membrane-bound viral proteins which proved able to elicit in vitro neutralizing or in vivo protective antibodies. Much emphasis was also given specifically to reference W which reports that the chimeric protein obtained by expression in E.coli of HSV gD coding gene (deleted of the carboxy-terminal end) and the ß-gal gene is able to raise anti-HSV1 and anti-HSV2 in vitro neutralizing antibodies.

8.3. The Opponent further objected to the novelty of the product claims directed to a vaccine on the basis of the disclosure in references L, N, K and in the EP-A-0 101 655 (reference E), that was considered during the examination proceedings under Art. 54(3) EPC.

Quite correctly the Opponent pointed out that the claimed vaccine cannot be regarded as defined or limited by the producing process; thus expression like "being the product of expression in or secretion from" or still "is a .. recombinant secretion product" are immaterial in defining the vaccine.
Based on this premise the synthetic peptide of L as well as the natural fragments of K and N are regarded as identical to the claimed vaccines, thus prejudicial for the novelty of the claims.
Emphasis was particularly given to L; in fact the peptide therein disclosed proved later (in 1985) to be immunoprotective in vivo (see reference S) and to the

EP-A-0 101655 which discloses inter alia a vaccine comprising the chimeric protein described in reference W and expressed in E.coli.

All the arguments against the novelty of any vaccine were however dropped after amendment of claims 10 and 11 by adding the feature "glycosylated" in relation to "truncated membrane-free derivative".

8.4. In contrast the arguments against the existence of an inventive step in the subject matter of the product claims were maintained.
The Opponent's position was that all the prior documents L, W, M, N and Q disclose candidate vaccines. Specifically the recombinant HSV gD chimeric peptide according to W and the synthetic peptide of L proved to be capable of eliciting in vitro neutralizing antibodies. This activity, as also admitted in the disclosure of the patent, is considered a very strong indication of an in vivo protective activity.
Thus confirming that the truncated peptide of the opposed patent also exhibit in vivo protective activity should be considered within the competence of the man of the art; thus not inventive.

8.5. The Opponent also objected to the claimed subject matter under Art.100(b) EPC, because the disclosure offers one example only of practical embodiment of the invention; namely only the protective activity of the truncated HSV gD is proved. Since, according to the Proprietor's position, such an activity cannot be predicted a priori for an expressed polypeptide, the Opponent concluded that patent does not provide the skilled person with the necessary means to repeat other embodiments of the invention.

Part II

Reasons for the Decision

1. The opposition is admissible because it meets all the requirements of Art.99(1) and 100 EPC and of Rules 1(1) and 55 EPC.

2.1 The amended claims are admissible in respect of Art. 123(2) EPC.
The amendments are supported by the following passages in the application as originally filed.
The amendments in claim 1, namely "viral" and "that raise neutralizing antibodies" instead of "capable of raising .." are supported by the items "Virus challenge" page 28 and "Immunisation of mice against HSV-2 infection" page 30, specifically by Table 1 and 2 at pages 28 and 31.
The addition of "glycosylated" in claims 10 and 11 is supported by page 1 line 29-31, page 4 line 21 to page 5 line 14, page 15 line 24-25, page 42 line 4 to page 43 line 12.
All the other amendments in claims 10 and 11 are directly taken from the original method-claims 14-20 or from the items "Virus challenge" page 28 and "Immunisation of mice against HSV-2 infection" page 30.

2.2. The amended claims are also admissible in respect of Art.123(3) EPC.
In fact the amendments offer a more closed and proper definition of the matter for which protection is sought, thus a limitation of the protection imparted by the granted patent.

3. The prior art

The quoted prior documents can be considered as belonging to the following groups:

References H, I and J disclose the expression in eukaryotic host cells of truncated membrane-free derivatives of membrane-bound viral polypeptides. The intended immediate purpose of the reported works is not the production of a vaccine. In fact the immunogenic activity of the secreted polypeptides is not tested: reference H only reports in the last paragraph of the article that "the work already accomplished .. may become a general method for obtaining with ease large quantities of purified eukaryotic membrane antigens for experimental analysis or vaccine production".

References N and K disclose the natural secretion of HSV-1 gD and gC fragments in the culture medium of HSV-1-infected eukaryotic cells. In N the fragments are recognized by anti-gD monoclonal antibodies and in K by an anti-gC monoclonal antibodies; thus the fragments are antigenically related to the corresponding gD and gC. In this case too, however the immunogenic activity of the fragments is not tested.

Reference W and E relate to the same experimental work, which is the expression of the HSV-1 gD in E. coli in the form of a chimeric protein comprising the carboxy-terminal free gD and ß-gal.
While in reference E (which is comprised in the state of the art pursuant Art. 54(3) EPC) there is reported the in vivo protective activity of said chimeric polypeptide, when formulated into a vaccine, in reference W

only the capability of raising in vitro neutralizing antibodies is tested.

References L, S and those enclosed to the Declaration of R.L. Burke as exhibits B, C and D disclose synthetic peptides which are immunogenic when bound to a carrier protein.
The peptide according to L comprises a determinant of the 12 Kd fragment at the amino terminus of HSV gD. The elicited polyclonal antibodies (antiserum) neutralize in vitro HSV. The same synthetic peptide was later proved (after the filing date of the opposed patent) to be also protective in vivo (reference S).
The peptide according to exhibits B, C and D show the ability of protecting in vivo an immunized animal, however they do not relate to HSV.

All the other cited documents are regarded as background documents less relevant than those discussed above.

4. Art. 100 (a) and 54 EPC.

4.1.1. The subject matter of claim 1 is a process which comprises producing a truncated polypeptide which raises neutralizing antibodies and which is protective in vivo. The production of said polypeptide is regarded as the intended purpose of the process. In order to achieve said purpose the process must necessarily comprise steps of testing the secreted polypeptides both for the in vitro neutralizing and in vivo protective activity.

In fact, though the complete surface protein in its natural environment is immunogenic and able to raise in vivo protective antibodies, the same protein, when expressed and secreted as truncated polypeptide by a host cell, does not automatically exhibit said properties. No

cited prior document would indeed prove this.
Admittedly the closest prior art (References H, I and J) describes processes for the expression and secretion in eukaryotic cells of truncated polypeptides which may, or may not, be structurally identical to the polypeptide produced according to claim 1.
However the purpose of said prior documents is to investigate the feasibility of a method for expressing viral surface proteins in a membrane free form; thus the purpose is other than producing polypeptide which maintain all the immunological properties of the native polypeptide and therefore which are still active as a vaccine.
For this reason none of the prior processes comprises testing the secreted polypeptide to ascertain whether they are immunogenic and whether the obtained antibodies (if any) are neutralizing and provide protection in vivo.
The process of claim 1 is thus regarded as novel over the disclosure in the aforementioned prior references.

4.1.2. References N an K have also been cited as disclosure prejudicial for the novelty of the process claims.

Reference N discloses the natural expression and secretion of gD fragments in the culture medium of eukaryotic cells infected by HSV-1. Reference K reports the same for HSV-1 gC.
On the basis of their reactivity with monoclonal anti-gD or anti-gC antibodies, the fragments are said to be immunologically related to the complete HSV-1 gD and gC.
However said antigenicity is not proved to correlate with an immunogenic activity. This is not the purpose of the two articles.
The two reported works represent in fact basic studies about the HSV-1 glycoproteins; thus the process therein

described does not, and could not comprise any steps of testing the immunogenic activity of the fragments. The process of claim 1 is therefore also recognized as novel over the disclosure in the aforementioned prior documents.

4.1.3. No other prior document was cited by the Opponent or considered relevant by the Division against the novelty of the process claims 1 to 9.

Therefore the subject matter of said claims meets the requirements of Art 54 EPC.

4.1.4. The Opponent's arguments were all based on the premise that the truncated polypeptides of the cited prior art are structurally identical to the polypeptide obtained by the process of the opposed patent. As a consequence said polypeptides should exhibit, though not stated in the prior references, the same immunogenic properties of the polypeptide at issue. Therefore the prior processes and the present one would be analogous processes intended for producing the same identical end-product; thus identical themselves.

Such arguments cannot be accepted by the Division. In fact no document has been provided which can render absolutely predictable that an immunogenic protein retains its immunogenic properties when expressed in and secreted from a heterologous system as a truncated polypeptide. Therefore "testing" the obtained product is a necessary step integrated in the claimed process but not contemplated by the prior processes.

4.2.1. The novelty of the product claims 10 to 12, which are directed to a vaccine, was also objected to.
Said vaccine comprises as active agent a glycosylated

truncated membrane-free derivative of a membrane-bound viral polypeptide. Said polypeptide being HSV-1 or-2 gD or gC; said derivative being capable of eliciting neutralizing antibodies which are protective in vivo against HSV-1 or -2.

4.2.2. Reference L, W, E, H, I, J, N and K were quoted during the proceedings as disclosures prejudicial to the novelty of the product claims.

A part from any consideration about the in vivo protective activity, the synthetic peptide of L is not said to be glycosylated.

The chimeric polypeptide of reference W and E is expressed in prokaryotic cells (E. coli); thus it cannot be glycosylated.

The truncated peptides according to reference H, I and J and N and K are expressed in eukaryotic cells, thus they could be glycosylated.

However a "vaccine" is a therapeutic composition which must comprise at least an active agent and an excipient and which must exhibit in vivo protective activity.

The aforementioned peptides are neither formulated into such a therapeutic composition nor are they proved to have any immunogenic, protective activity. Therefore references H, I, J, N and K anticipate at the best some "candidate active agents" which however cannot yet be regarded as active agents, let alone as vaccines.

The Opposition Division is therefore of the opinion that none of the cited prior document anticipates the vaccine of claims 10 to 12.

5. Art. 100 (a) and 56 EPC

5.1. For the purpose of Art. 56 EPC the Opponent has

cited and discussed the references H, L, W, N, K and Q. Reference H was however indicated as the closest prior art, that should be read in combination with reference L. During the Oral Proceedings reference W was also discussed as a very relevant prior art.

The Division accepts the Opponent's selection of cited documents.

The author of reference H reports, in the last paragraph of the Discussion (page 603), that the method therein disclosed may become a general method for preparing membrane antigens for vaccine production. This conclusion is however regarded as speculative, since the work reported in H absolutely does not contemplate any evaluation or allegation about the immunogenic properties of the expressed polypeptide derivatives, let alone about a protective activity. It must be noted that the immunoprecipitation carried out with anti-HA (whole polypeptide) in order to isolate the fragments merely proves an antigenic correlation to the native polypeptide; however it does not highlight any immunogenic ability.

References I and J, which are nearly equivalent to H, are still poorer of details than H about the immunogenicity of the derivatives therein described.

5.2. The gap between the process of the opposed patent and that described in H consists of the additional steps of testing the immunogenic properties of the secreted peptides to investigate whether they are capable of raising an in vivo protective antibody-response, or to determinate which one exhibits said property.

5.3. Therefore the technical problem underlying the present

invention can be recognized in demonstrating the suitability of the process according to reference H for producing polypeptide derivatives which can be employed as active constituents of vaccines; stated in other words the problem consists in proving that the polypeptide derivatives produced by the process according to H retain all those immunological properties which are necessary for formulating a vaccine.

5.4. The Division admits that the physical action of testing the immunological properties of a polypeptide falls within the competence of any practitioner. This opinion was strongly asserted by the Opponent. However this is not sufficient to deny the existence of an inventive merit.
The important question is in fact whether the skilled person, in the attempt to demonstrate the ability of an expressed truncated derivative of a viral protein to elicit in vivo protective antibodies against the pathogen bearing the whole protein, would have, or not, a reasonable expectation of success.

In practice the expressed truncated derivative must not only retain the amino acid sequence of the native protein but it must be able to fold in the correct spatial conformation in order to expose the same determinants as the native protein.

5.5. Would the prior documents cited in the proceedings support said expectation of success ?
The Division is not of this opinion, on the basis of the document analysis which follows.
An inventive step (if any) involved in the process at issue must necessarily be discussed bearing in mind whether the obtained product actually involves an inventive step.

5.5.1. Reference L discloses the identification of an HSV gD determinant capable of stimulating neutralizing antibodies and the production of a synthetic 16 mer peptide which comprises said determinant.
This 16mer peptide, which is not immunogenic per se, when coupled to a strong immunogenic carrier (KLH), proved able to raise anti-HSV neutralizing antibodies (in vitro).
First of all a synthetic process is not comparable to the expression of a product by DNA technology.
Moreover the described complex is not structurally correlated to the derivatives obtained by the claimed process (inter alia the 16 mer is not glycosylated).
Furthermore the ability of the elicited antisera to neutralize in vitro HSV is no proof that the same antisera are protective in vivo.
That a vaccine candidate, like the peptide of L, does not necessary prove to be suitable as a vaccine upon in vivo experimentation was also confirmed by R.L. Burke (expert) during the oral proceedings.

Thus the Division considers that reference L could not be regarded as a support enabling the skilled person, while testing the immunogenic properties of the polypeptide derivatives prepared by the process of H, to predict their protective activity.

5.5.2. Not more relevant is regarded by the Division the combination of reference H with the teaching of any one of the articles enclosed as exhibit B, C and D to the R. L. Burke Declaration.
The synthetic short peptides therein described are not glycosylated and are not immunogenic per se. Only in the form of a conjugate with a strongly immunogenic carrier they are capable of raising an in vivo protective re-

sponse.

5.5.3. Reference W describes the expression in E.coli of a chimeric protein consisting of the HSV-1 gD (deleted of the carboxy-terminus) and the ß-gal.
Unlike the derivative of the opposed patent, the chimeric protein of W is not glycosylated, since expressed from prokaryotic cells, therefore it is structurally different from the present derivatives.
Said chimeric protein is actually immunogenic and able to raise in vitro neutralizing antisera; however, and as already stressed for reference L, said property is not a proof that the same antisera are also protective in vivo.

Thus reference W teaches, like reference L, only the in vitro activity of a polypeptide structurally different from the derivative of the opposed patent.

In a further approach to reference W, the Opponent indicated such a prior art as relevant per se regardless of any combinations with other prior art.
The Division however notes that the process therein disclosed does not result in a product which can be recovered from the culture medium as inherent in the present process, but on the contrary the expressed product is recovered upon lysis of the host cell and purification of the desired product from the E. coli material (see Fig.3 page 74).
This feature of the claimed process, combined with the retention of the protective immunogenic activity of the expressed product is not derivable from reference W and therefore it constitutes an inventive step over the teaching in said prior document.

5.5.4. Other prior documents have been also considered by

the Opponent: namely references N and K.
The relevance of the teaching in said articles depends on a specific interpretation given to the wording of claim 1 by the Opponent.
According to said interpretation the process of claim 1 does not necessarily imply the expression of a "truncated DNA" in order to obtain a truncated polypeptide.
The case where a full length protein is expressed from a complete structural gene and subsequently cleaved by the cellular proteolytic enzymes during secretion is said to be also contemplated by the wording of claim 1.
The Opponent also argued that the word "transfected" in claim 1 comprises in its meaning any "viral infection".

Without entering in the merit of the reliability of said interpretation, the Division needs only to point out that, as a matter of fact, the above cited articles do not teach anything closer to the present process than reference H. Thus combination of N or K to any one of the above discussed documents would lead, at the best, to the same conclusion.

Therefore none of the quoted prior art taken alone or in combination deprive the process of claim 1 of an inventive step.

6. The Division also recognized the presence of an inventive step in the subject matter of product claims 10 to 12, which are directed to a vaccine comprising, as active agent, a glycosylated truncated membrane-free derivative of the membrane-bound HSV-1 or-2 gD and gC.
The reasons have already been partially presented in discussing the inventive step involved in the process claims.

6.1. The Opponent mainly argued that the <u>in vitro</u> neutral-

izing activity shown by the antibodies elicited by a candidate vaccine (in the present instance those of reference L, W , N and Q) is recognized by the skilled person as a very strong indication of the in vivo protective activity, and that confirming said activity does not involve an inventive step.

For this purpose the Opponent cited the later published (Dec. 1985) reference S which reports the in vivo protective activity of the synthetic peptide of reference L, or reference Q where apparently the in vitro neutralizing activity was considered predictive of the in vivo protection.

7.2. Such arguments cannot be accepted by the Division who considers that, though the in vitro activity may be an indication of the in vitro protection, it cannot be regarded as a proof or a certainty of said activity.
It has already stressed that the determining point in recognizing the existence of an inventive step in the solution to the underlying technical problem was not whether the physical action of testing the activity of a candidate vaccine in an animal model is, or is not, within the competence of the skilled person, but whether in performing this "obvious" activity he would be able to predict the result of said activity.

7.3. That a candidate vaccine does not necessarily turn out to be a vaccine was also confirmed by R.L. Burke who presented during the Oral Proceedings the general working scheme followed to develop a vaccine.
The fifth stage of this scheme contemplates :
Testing immunogenicity with regard to neutralizing ABs (in vitro);
Evaluating protection in animal models;
Evaluating protection in humans.

R.L. Burke, who was present as an expert in the technique of developing vaccines, was not able to indicate which percent of candidate vaccines (neutralisation in vitro) can be expected to be positive in animal model. She confirmed that this result cannot be predicted and can only be confirmed experimentally each time for each candidate.

7.4. Moreover the Division needs to point out that among all the cited prior documents, references L, W and Q only disclose polypeptide derivatives proved to raise at least an in vitro activity; those derivatives however are all structurally different from the derivatives of the opposed patent, either because not glycosylated or because not truncated.
On the contrary not even an in vitro result is reported in the prior art in relation to those derivatives which are structurally comparable to those of the patent (H, I, J, N, and K).

The vaccine of claims 10 to 12 is therefore not obviously derivable from the teaching of any cited prior document. Thus it is recognized as involving an inventive step.

8. Art. 100 (b) and 83 EPC

8.1. The Opponent objected to the subject matter of the opposed patent for insufficiency of disclosure.
By referring to the difficulties existing in predicting the results of an expression/secretion process and the activity of the obtained product, the Opponent concluded that only the embodiment of the invention which is disclosed by way of examples, namely a process for producing truncated gD and a vaccine comprising the truncated

gD, should be allowed pursuant Art. 83 EPC. Any further embodiment relative to other derivatives would be arbitrary since the disclosure does not enable its repeatability.

8.2. The Division rejects said arguments according to a consolidated practice of the EPO based on the Decision of the Technical Board of Appeal T 292/85.

The Division accepts that, before the present patent, the effectiveness of the present process and vaccine was not predictable; however once the theory behind the invention is proved to be reliable, the reduction to practice of the same concept in different embodiments does not require any activity beyond the competence of any practitioner.
One embodiment of the present invention is properly exemplified (process and vaccine concerning HSV gD); this is regarded by the Division as sufficient to meet the requirements of Art. 83 EPC.

9. The Opposition Division is therefore of the opinion that, taking into account the amendments made, the patent and the invention to which it relates meet the requirements of the EPC.

ANNEX I

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